PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To:

GANGULI, Dr. Prabuddha
"Vision" -IPR", 103B Senate
Lokhandwala Township, Akurli Road
Kandivali East, Mumbai-400 101
INDE

Date of mailing *(day/month/year)*	20/01/2004
Applicant's or agent's file reference: TLP/533/PCT1	REPLY DUE: within 2 / 00 months/days from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN02/00207	14/10/2002	17/06/2002

International Patent Classification (IPC) or both national classification and IPC

A61K9/20

Applicant

THEMIS LABORATORIES PRIVATE LIMITED

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 17/10/2004

Name and mailing address of the IPEA/

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+ 31-70) 340-2040
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Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+ 49-89) 2399 2828

I. Basis of the opinion

1. The basis of this written opinion is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claims references).

2. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

Dr. Prabuddha Ganguli, Advisor
VISION-IPR
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12th March 2004

To,
European Patent Office,
IPEA, P.B. 5818 Patentlaan 2,
NL – 2280 HV Rijswijk
Netherlands

Sub: Reply to first written opinion dated 20th Jan 2004.
Re: International Application No. PCT / IN02 / 00207
Applicant: Themis Laboratories Private Limited et. al.,

Dear Sir,

This is with reference to your letter dated 20th January 2004 enclosing the written opinion on our PCT application.

We have studied the contents of the opinion and have amended the claims and complete specification.

As required by rule 66.8 we enclose herewith the replacement sheet of the patent application (annex 1) together with the citations and explanations (annex 2)

Kindly take these in record and proceed with further examination of the application.

We hope you will find these in order and request you to give us your second written opinion.

Regards,

Prabuddha Ganguli
Patent Agent on record
(TLP / 533 / PCT1)
Applicants / Agents File Reference No.
Enclosure:
Annex 1: Replacement Sheets 4, 18, 19, 21 and 22.
Annex 2: Pages 1 – 5

Annex 2

PCT APPLICATION: PCT / IN02 / 00207

Applicant: Themis Laboratories Private Limited et. al.,

Applicants or Agents File Reference No. TLP / 533 / PCT1

Written Explanation as Per Rule 66.8

The following pages have been incorporated as replacement sheets (Sheets 4, 18, 19, 21 and 22) on account of an amendment. The differences between the replaced sheets and the replacement sheets and the reasoned statements following the amendments are as follows.

Table indicating the page number on which amendments are done and replaced by replacement sheet

Original application	Amended Specification
Page No. 1 – 3	AS ORIGINALLY FILED (Sheet not enclosed)
Page No. 4	**Replaced by replacement sheet of page no. 4 as enclosed**
Page No. 5 – 17	AS ORIGINALLY FILED (Sheet not enclosed)
Page No. 18	**Replaced by replacement sheet of page no. 18 as enclosed**
Page No 19	**Replaced by replacement sheet of page no. 19 as enclosed**
Page No. 20	AS ORIGINALLY FILED (Sheet not enclosed)
Page No 21	**Replaced by replacement sheet of page no. 21 as enclosed**
Page No 22	**Replaced by replacement sheet of page no. 22 as enclosed**
Abstract on Page No. 23	AS ORIGINALLY FILED (Sheet not enclosed)

A) Following amendments under Article 34, have been incorporated in the application as originally filed by way of typographical corrections and clarification.

1. Line 22 on page 4, "multiplayer" is replaced by "multilayer" to read as "and methods of manufacturing of **multilayer** tablets with such characteristics" (typographical error).

B) The following amendments have been made in the claims of the application as originally filed.

1) **Claim 1** of the **application as originally filed** on **page no. 18** has been replaced by

We Claim:

"A process for manufacture of multi-layered tablet dosage of antihyperglycemic pharmaceutical compositions for once a day administration comprising:

a) preparation of type I granules comprising atleast one non-biodegradable inert polymer and atleast 48% of biguanide or its pharmaceutically acceptable salts such as Metformin HCl of particle size less than 100 microns followed by treatment with lubricants to achieve pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salt;

b) preparation of type II granules comprising active pharmaceutical ingredient (API) or APIs or their pharmaceutical acceptable salts selected from the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers followed by treatment with lubricants to achieve immediate release of said API;

c) compressing the type I granules and type II granules to obtain layered tablets.

This appears on **page no. 18 of the amended specification as Claim 1** by way of correction, clarification and explanation. The present construction clearly brings out the novelty and inventive step.

2) **Claim 2 and claim 3** of the **application as originally filed** on **page no. 18** have been deleted as the irrelevant claims in the amended specification is superfluous.

3) **Claim 4** of the **application as originally filed** on **page no. 18,** "Pioglitazone HCl and are present in amount from about 5%" **is replaced by** "Pioglitazone HCl present in amounts from about 5%" by way of clarification and explanation.

This appears on **page no. 18 of the amended specification as Claim 4.**

4) **Claim 5** of the **application as originally filed** on **page no. 18-19** has been replaced by

" A process as claimed in claim 1 wherein,

a) atleast 48% and preferably over 50% of the formulation composition comprises of a biguanide such as Metformin HCl of particle size less than 100 microns;

b) Metformin HCl is blended with non-biodegradable, inert polymer, blending carried out in mixers such as planetary mixers, octagonal blenders, V-blenders or rapid mixer granulators or fluid bed granulators;

c) the Metformin HCl - polymer blend is wet granulated using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent being water or hydroalcoholic solution.

d) the granulated mass is dried followed by sizing using comminuting mill such as Fitz mill or oscillating granulator or any other equipment suitable for the purpose, with appropriate mesh preferably around 1-mm mesh.

e) the granules thus produced are mixed with Talc, magnesium stearate and colloidal silicon dioxide.

This appears on **page no. 18 – 19 of the amended specification as Claim 5** by way of clarification and explanation.

5) **Claim 17** of the **application as originally filed on Page no. 21,** "A process for the composition as claimed in claims 1-6, 16" is replaced by **"A process for the composition as claimed in claims 1, 4 – 6, 16"** by way of correction and clarification. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 17 on page no. 21 of the amended specification**.

6) **Claim 18** of the **application as originally filed on Page no. 21,** "A process according to claims 1 – 6" is replaced by "**A process according to claims 1, 4 – 6"** by way of correction and clarification. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 18 on page no. 21 of the amended specification**.

7) **Claim 19** of the **application as originally filed on Page no. 21,** "A process according to claims 1,2,5" is replaced by **"A process according to claims 1 and 5"** by way of correction and clarification. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 19 on page no. 21 of the amended specification**.

8) **Claim 20** of the **application as originally filed on Page no. 21,** "A process according to claim 1 – 19" is replaced by **"A process according to claims 1, 4 – 19"** by way of correction and clarification. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 20 on page no. 21 of the amended specification**.

9) **Claim 21** of the **application as originally filed on Page no. 21,** "A process for the manufacture of composition as claimed in claims 1 – 20" is replaced by **"A process for the manufacture of composition as claimed in claims 1, 4 – 20"** by way of correction and clarification. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 21 on page no. 21 of the amended specification**.

10) **Claims 22** of the **application as originally filed on page no. 21,** "A process for the manufacture of composition as claimed in claims 1– 20" is replaced by **"A process for the manufacture of composition as claimed in claims 1, 4 – 20"** by way of correction and clarification. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 22 on page no. 21 of the amended specification.**

11) **Claim 23** of the **application as originally filed on page no. 21,** "A process according to claims 1– 22" is replaced by "**A process according to claims 1, 4 – 22"** by way of clarification and correction. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 23 on page no. 21 of the amended specification.**

12) **Claim 24 on page no. 21,** "pharmaceutically acceptable salts claimed in claims 1, 2, 5, 7 – 15, 18 – 19" is replaced by "**pharmaceutically acceptable salts claimed in claims 1, 5, 7 – 15, 18 – 19"** by way of clarification and correction. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 24 on page no. 21 of the amended specification.**

13) **Claim 25** of the **application as originally filed on page no. 22,** "pharmaceutically acceptable salts claimed in claims 1, 3 – 4, 6, 16, 18" is replaced by "**pharmaceutically acceptable salts claimed in claims 1, 4, 6, 16, 18"** by way of clarification and correction. It may be noted that the claims 2 and 3 of the application as originally filed have been deleted. This appears in **claim 25 on page no. 22 of the amended specification.**

14) **Claim 26** of the **application as originally filed** on **page no. 22** has been replaced by "A multi-layer tablet dosage comprising atleast two layers wherein,

a) type I layer comprising atleast one non-biodegradable inert polymer and biguanide such as Metformin HCl of particle size less than 100 microns resulting in pH independent prolonged in – vitro release of the biguanide;

b) another layer comprising of active pharmaceutical ingredients (API) or APIs and their pharmaceutically acceptable salts to be immediately released, belonging to the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers."

This appears on **page no. 22 of the amended specification as Claim 26. The present construction clearly brings out the novelty and inventive step.**

15) **Claim 27** of the **application as originally filed** on **page no. 22** has been replaced by "A pharmaceutical composition claimed in claim 26 in which the prolonged release pharmaceutical ingredient belongs to the group of biguanide such as Metformin HCl and the immediate release active pharmaceutical ingredient belongs to the group of thiazolidinediones such as Pioglitazone HCl and/or biguanides such as Metformin HCl".

This appears on **page no. 22 of the amended specification as Claim 27 by way of correction and clarification.**

16) **Claim 30** of the **application as originally filed** on **page no. 22** has been deleted as the as the irrelevant claim in the amended specification is superfluous.

17) **Claim 31** of the **application as originally filed on page no. 22,** "A composition as claimed in any one of claims 26-30 wherein" is replaced by "**A composition as claimed in any one of claims 26-29 wherein"** by way of clarification and correction. It may be noted that the claims 30 of the application as originally filed has been deleted. This appears in **claim 31 on page no. 22 of the amended specification**.

18) **Claim 32** of the **application as originally filed on page no. 22,** "A composition as claimed in claims 26 –31" is replaced by **"A composition as claimed in claims 26 – 29, 31"** by way of clarification and correction. It may be noted that the claims 30 of the application as originally filed has been deleted. This appears in **claim 31 on page no. 22 of the amended specification**.

19) **New claim - Claim 33** on **page no. 22** has been added to read as:

"A pharmaceutical composition comprising granules of Metformin HCl prepared as per claim 1, capable of being compressed into tablet dosage exhibiting pH independent in-vitro release of Metformin HCl atleast for a period of 8 hours comprises Metformin HCl of particle size less than 100 microns and atleast one non-biodegradable, inert polymer."

This appears on **page no. 22 of the amended specification as Claim 33** as the granules comprising Metformin HCl and non – biodegradable inert polymer is capable of being compressed into single tablet dosage form that exhibits pH independent in – vitro release of Metformin HCl atleast for a period of 8 hours.

20) **Claims 6 – 9 on page no. 19, claims 10 – 15 on page no. 20 and 21, Claim 16 on page no. 21 and Claims 28 – 29** on **page no. 22** of the application as originally filed remains unchanged.

ANNEX 1

PCT Publication No. WO9947128 describes the preparation of Metformin HCl controlled release tablet using biphasic delivery where Metformin HCl is blended with a hydrophilic or hydrophobic polymer to form granules, which are further dispersed or embedded in one or more hydrophilic or hydrophobic polymer or material. However if these biphasic granules are to be used for the preparation of bilayered tablets of Metformin HCl and sulfonyl urea or thiazolidinedione, the size of the tablet becomes relatively large causing inconvenience in swallowing.

Marketed antidiabetic combination preparation is Glucovance RTM, of Bristol Myers Squibb (Physician Desk Reference, Ed.55, Pg. 3477), which comprises of Metformin HCl and Glyburide as a single integral unit immediate release tablet.

Thus there is no prior art that teaches patient-convenient cost effective pharmaceutical compositions and the manufacture of granules containing biguanide capable of being compressed into tablets with pH independent prolonged release of the biguanide. Further the prior art does not teach compositions and manufacture of granules containing biguanide capable of being compressed into bilayered tablets with the other layer comprising of active pharmaceutical ingredients belonging to class of thiazolidinedione, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers for desired layer-selective immediate release of these active pharmaceutical ingredients and pH independent, prolonged in-vitro release of biguanide. The prior art also does not teach compositions and methods of manufacturing of multilayer tablets with such characteristics.

Objects of the invention:

The object of the invention is to provide process for the manufacture of patient convenient, cost effective antihyperglycemic pharmaceutical compositions in multi-layered tablet dosage form capable of layer-selective prolonged release of one active pharmaceutical ingredient(s) in the group of biguanides and layer-selective of immediate release of another active pharmaceutical ingredients belonging to the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers.

CLAIMS.

We claim:

1. A process for manufacture of multi-layered tablet dosage of antihyperglycemic pharmaceutical compositions for once a day administration comprising:

a) preparation of type I granules comprising atleast one non-biodegradable inert polymer and atleast 48% of biguanide or its pharmaceutically acceptable salts such as Metformin HCl of particle size less than 100 microns followed by treatment with lubricants to achieve pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salt;

b) preparation of type II granules comprising active pharmaceutical ingredient (API) or APIs or their pharmaceutical acceptable salts selected from the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers followed by treatment with lubricants to achieve immediate release of said API;

c) compressing the type I granules and type II granules to obtain layered tablets.

2. Deleted

3. Deleted

4. A process for the manufacture of composition as claimed in claim 1 wherein layer-selective immediate release of thiazolidinediones where the said thiazolidinediones is but not limited to Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts thereof such as Pioglitazone HCl present in amounts from about 5% to about 30% by weight of the corresponding layer.

5. A process as claimed in claim 1 wherein,

a) atleast 48% and preferably over 50% of the formulation composition comprises of a biguanide such as Metformin HCl of particle size less than 100 microns;

b) Metformin HCl is blended with non-biodegradable, inert polymer, blending carried out in mixers such as planetary mixers, octagonal blenders, V-blenders or rapid mixer granulators or fluid bed granulators;

c) the Metformin HCl - polymer blend is wet granulated using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent being water or hydroalcoholic solution.

d) the granulated mass is dried followed by sizing using comminuting mill such as Fitz mill or oscillating granulator or any other equipment suitable for the purpose, with appropriate mesh preferably around 1-mm mesh.

e) the granules thus produced are mixed with Talc, magnesium stearate and colloidal silicon dioxide.

6. A process as claimed in claim 1 wherein :

- The particle size of Pioglitazone HCl used is less than 30 microns.
- the pioglitazone HCl is blended with fillers, disintegrants, binders, lubricants and permitted colours carried out in planetary mixer, octagonal blender, double cone blender, rotary mixer granulator, drum mixer, ribbon blender, fluid bed processor or any other suitable mixer.

7. A process as claimed in claim 5, wherein the non-biodegradable, inert polymers are selected from the group consisting of cellulose derivatives, (meth)acrylic acid co-polymers, Xanthan gum, Guar gum, Alginates and their acceptable salt thereof.

8. A process as claimed in claim 7, wherein the non-biodegradable, inert polymers are selected from a minimum of one or more cellulose derivative or combination of cellulose derivatives with (meth)acrylic acid co-polymers or combination of cellulose derivatives with alginates and /or (meth)acrylic acid co-polymers or combination of cellulose derivatives with Xanthan gum or combination of cellulose derivatives with guar gum.

9. A process as claimed in claim 7- 8, wherein the cellulose derivative is alkylcellulose and/or hydroxyalkylcellulose and/or carboxyalkylcellulose, the (meth)acrylic acid co-polymers are selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt.

than 1500cP.; sodium carboxymethylcellulose is not less than 1500 cP and xanthan gum is not less than 1200 cP.

16. A process as claimed in claims 1, 4, 6 wherein the disintegrating agents are selected from the group comprising starch, sodium starch glycollate, crosscarmellose sodium, crosspovidone, pregelatinized starch, microcrystalline cellulose, hydroxypropylcellulose.

17. A process for the composition as claimed in claims 1, 4 – 6, 16 wherein the immediate release layer containing a combination of thiazolidinediones and biguanides with the excipients and other formulation ingredients comprises about 5% to about 30% by weight of the thiazolidinediones and about 1 to about 10% of biguanides.

18. A process according to claims 1, 4 - 6 where Metformin HCl is in the range of 500mg -2000mg and Pioglitazone HCl equivalent to Pioglitazone is in the range of 15 - 60 mg.

19. A process according to claims 1 and 5 wherein the granules of the biguanide prolonged release layer formed can be stored for prolonged period without change in compression characteristic.

20. A process according to claims 1, 4 – 19 wherein, the bilayer tablet formed has hardness in the range of about 6 to about 12 kg/ Sq. cm, low friability of <1% without capping.

21. A process for the manufacture of composition as claimed in claims 1, 4 – 20 wherein the layers of the tablet are parallel to each other.

22. A process for the manufacture of composition as claimed in claims 1, 4 – 20 wherein one layer is only partially covered by the next layer.

23. A process according to claims 1, 4 – 22 wherein, the multilayer tablet is enrobed by soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile.

24. A process for manufacture of granules containing biguanide as or its pharmaceutically acceptable salts claimed in claims 1, 5, 7 – 15, 18 - 19 capable of being compressed to a tablet dosage form with pH independent prolonged release of biguanide at the end of 1, 4, and 8 hours lies in the range of 25 – 45%, 50 – 80% and not less than 75% respectively.

25. A process for manufacture of granules containing active pharmaceutical ingredients (API) or their pharmaceutically acceptable salts claimed in claims 1, 4, 6, 16, 18 capable of being compressed to a tablet dosage form with immediate release of the same is not less than 80 % at the end of 30 minutes.

26. A multi-layer tablet dosage comprising atleast two layers wherein,

a) type I layer comprising atleast one non-biodegradable inert polymer and biguanide such as Metformin HCl of particle size less than 100 microns resulting in pH independent prolonged in – vitro release of the biguanide;

b) another layer comprising of active pharmaceutical ingredients (API) or APIs and their pharmaceutically acceptable salts to be immediately released, belonging to the group of thiazolidinediones, sulfonyl ureas, alpha - glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor, LDL catabolism enhancers.

27. A pharmaceutical composition claimed in claim 26 in which the prolonged release pharmaceutical ingredient belongs to the group of biguanide such as Metformin HCl and the immediate release active pharmaceutical ingredient belongs to the group of thiazolidinediones such as Pioglitazone HCl and/or biguanides such as Metformin HCl.

28. A composition as claimed in claim 26-27 wherein the immediate release API or APIs are present in an amount of from 5%-30% by wt.

29. A composition as claimed in claims 26-28 wherein the immediate release layer containing a combination of thiazolidinediones and biguanides with the excipients and other formulation ingredients comprises about 5% to about 30% by weight of the thiazolidinediones and about 1 to about 10% of biguanides.

30. Deleted

31. A composition as claimed in any one of claims 26-29 wherein layer-selective immediate release of thiazolidinediones where the said thiazolidinediones is but not limited to Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts thereof such as Pioglitazone HCl.

32. A composition as claimed in claims 26 – 29, 31, wherein the prolonged release layer contain Metformin HCl and the immediate release layer contain Pioglitazone HCl.

33. A pharmaceutical composition comprising granules of Metformin HCl prepared as per claim 1, capable of being compressed into tablet dosage exhibiting pH independent in-vitro release of Metformin HCl atleast for a period of 8 hours comprises Metformin HCl of particle size less than 100 microns and atleast one non-biodegradable, inert polymer.

PATENT COOPERATION TREA

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GANGULI, Dr. Prabuddha
"Vision" -IPR", 103B Senate
Lokhandwala Township, Akurli Road
Kandivali East, Mumbai-400 101
INDE

PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	30.06.2004
Applicant's or agent's file reference	REPLY DUE: **within 1 month(s)** from the above date of mailing
TLP/533/PCT1	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 0200207	14.10.2002	17.06.2002

International Patent Classification (IPC) or both national classification and IPC
A61K9/20

Applicant
THEMIS LABORATORIES PRIVATE LIMITED

1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 17.10.2004

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
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Authorized Officer
Rankin, R

Formalities officer (incl. extension of time limits)
Wallentin, M
Telephone No. +31 70 340-3991

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-3, 5-17	as originally filed
4	received on 15.03.2004 with letter of 12.03.2004

Claims, Numbers

1-30	received on 15.03.2004 with letter of 12.03.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-30
Inventive step (IS)	Claims	1-30
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: WO 01/35941 A (LILLIOTT NICOLA JAYNE ;MACKENZIE DONALD COLIN (GB); SMITHKLINE BEE) 25 May 2001 (2001-05-25)

1 Amendments

The amendments filed with the International Bureau under Article 19(1) with the letter of 12th March 2004 meet the requirements of Article 19(2) PCT.

2 Article 6 PCT

2.1 The applicant is requested, in future to renumber both the claims in sequential order and also to correctly renumber the claim dependencies . At present, deleted claims have retained their old numbering and it is not entirely clear if the claim dependencies are as the applicant intends or not. These deficiencies result in the claims as a whole being unclear (Article 6 PCT). The applicant is asked to rectify these issues when filing any amended claims.
The claim numbers mentioned in this communication, are renumbered the claims - ie deleted claims are ignored and not given a number.

2.2 In claims 1, 17, 18, 20, 22-25 and 30 the applicant attempts to define subject matter in terms of the effect to be achieved, thus merely reiterating the desired effect of the invention. Such phraseology is unclear and in breach of Article 6 PCT. The applicant may only define the invention in terms of the technical features which contribute to the solving of the problem faced. The applicant, when redrafting claims should be careful to include only technical features in the claims rather than speculative statements of the type mentioned in the above claims.

2.3 Claims 1, 3 5-8, 24, 34 are unclear (Article 6 PCT) for the following reasons:
A compound may not be defined according to its mode of action as is done with terms such as "inhibitor" or "enhancer" (Article 6 PCT). Terms such as "antihyperglycemic pharmaceutical compositions" defining unnamed compounds according to their desired pharmaceutical profiles are also not acceptable under Article 6 PCT. The undefined terms "non-biobegradable, inert polymer" and "cellulose derivative" are also unallowable since they too are extremely broad in slope.
Defining compounds in such ways result in unclarity in the claims since it is not possible

to determine what the applicant seeks to protect. These terms are so broad and so vague that that any number of agents may fall within these definitions, including compounds which have not yet been invented. The applicant therefore seeks protection for compositions containing molecules which have not yet been invented, which us not permissable (Article 6 PCT)
It is impossible for the skilled person to know with any certainty what the applicant seeks to protect with these terms and he or she would be faced with the undue burden to test all known compounds to determine the scope of the claims. It is also not possible to establish the novelty or otherwise of such claims due to the presence of these unclear terms which could well cover thousands of molecules (Article 33(2) PCT.

2.4 The application furthermore lacks comlete disclosure due to the presence of these unclear and unduely broad terms (Article 5 PCT). The claims must contain suficient technical disclosure of the solution to the problem. It would be an undue burden for the skilled person to characterise all compounds falling under the above broad terms to ascertain if they would be compatible with the tablet formulations of the application.

2.5 The claims are also not fully supported (Article 6 PCT) due to the presence of these unclear and unduely broad terms because application does not enable the skilled person is unable to carry out the invention over the whole fo the claimed area.

2.6 Given the breadth of these terms within the claims, the inventive step of the claims is also called into question since it is purely speculative to assume that all compounds falling under the vague definitions would contribute to the solving of the problem adressed in the application (Article 33(3) PCT.
The claims affected by the objections above are: 1, 3 5-8, 24, 34. These objections may be overcome by the replacement of these terms by appropriate compound names.

2.7 The use of the terms "and/or", "but not limited to", "such as" all introduce unclarity into the claims since by their unlimited nature, make it impossible for the skilled person to determine what subject matter is sought for protection (Article 6 PCT). The applicant must remove these terms from claims 1-3, 6, 25, 31, to overcome this objection.

2.8 In claims 2, 9, 10, 15, 18 and 27 the applicant refers to ranges of values in terms which render said claims unclear. Use of the word "about" with reference to these ranges it not allowable since the degree of uncertainty thus introduced makes it impossible for the skilled person to ascertain what is sought for protection.

2.9 Claim 1 is unclear (Article 6 PCT) because the reference to "at least 48% of biguanide" in the fourth line does not state if the 48% is by weight or volume. The same deficiency is present in claim 5

3 **Article 33(2) PCT**

3.1 The prent application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-30 is not new in the sense of Article 33(2) PCT.

3.2 The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-30 is not new in the sense of Article 54(1) and (2) EPC.

3.3 The document D1 discloses (page 2 line 8 to page 3, line 39; page 4, lines 15-26; examples 2, 5-9 and 25) processes for the manufacture of multi-layered tablet dosages of the biguanide compound metformin and a thiazolidinedione compound. Granules of the metformin are in a prolonged release form and the thiazolidinedione granules are for immediate release. Granules are screened and sized, treated with lubricants and compressed into layered tablets.

3.4 The applicant is reminded that the unclarities inthe claims may compromise the novelty of the claims if unduely broad terms are used instead of technical terms.

12th July 2004

To,
Rankin, R.
EPO, IPEA, P.B. 5818 Patentlaan 2,
NL – 2280 HV Rijswijk
Netherlands

Sub: Second Written Opinion Dated 30th June 2004.
Re: International Application No. PCT / IN02 / 00207
Applicant: Themis Laboratories Private Limited.

Dear Sir,

We have received your 2nd written opinion on our PCT application PCT / IN02 / 00207.
We thank you for your detailed explanation and we are in the process of amending our claims. We would like to seek some clarification from you on the written opinion.

The written opinion in paragraph 2.3 refers to claims 1,3, 5 – 8, 24 and 30 stating that they are not clear. We would like to indicate that the formulations disclosed in the present invention are indeed "***antihyperglycemic composition***" and this is a standard terminology used in the pharmaceutical industry. Similarly terms such as "***alpha - glucosidase inhibitor, aldose reductase inhibitor, squalene synthesis inhibitor, angiotensin converting enzymes inhibitor, LDL catabolism enhancers***" are also standard terms. Our formulation and process does indeed cover any of the compounds from the family of such compounds.

We therefore seek further clarification from you whether we need to define entire class of compounds that fall within this family of compound in which case we will have to literally list hundreds of compounds.

We should be grateful if you could kindly send us the clarification of the above to enable us to respond to the written opinion.

Regards,

For Themis Laboratories Private Limited
Janak R. Shah (Applicant)
(TLP / 533 / PCT1)
Applicants / Agents File Reference No.

Vision PR
Consulting in : Management of Intellectual Property Rights • Information Security • Knowledge Management

21st July 2004

To,
Rankin, R.
European Patent Office,
IPEA, P.B. 5818 Patentlaan 2,
NL – 2280 HV Rijswijk
Netherlands

Sub: Reply to second written opinion dated 30th June 2004.
Re: International Application No. PCT / IN02 / 00207
Applicant: Themis Laboratories Private Limited et. al.,

Dear Sir,

This is with reference to your letter dated 30th June 2004 enclosing the second written opinion on our PCT application.

We have studied the contents of the opinion and have amended the claims and complete specification.

As required by rule 66.8 we enclose herewith the replacement sheet of the patent application (annex 1) together with the citations and explanations (annex 2).

Kindly take these in record and proceed with further examination of the application.

We hope you will find these in order and request you to give us your final opinion.

Regards,

Prabuddha Ganguli
Patent Agent on record
(TLP / 533 / PCT1)
Applicants / Agents File Reference No.
Enclosure:
Annex 1: Replacement Sheets 18 – 24
Annex 2: Pages 1 – 11
Reference

CLAIMS.

We claim:

1. A process for manufacture of antihyperglycemic pharmaceutical composition as multi-layered tablet dosage form for once a day administration comprising:

• preparation of type I granules for pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts wherein, the type I granules comprise atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns, blended with one or more polymers selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide or its pharmaceutically acceptable salts;

• preparation of type II granules for immediate release of active pharmaceutical ingredient (API) or APIs or their pharmaceutical acceptable salts selected from thiazolidinediones and sulfonyl ureas wherein, the said API or APIs or their pharmaceutical acceptable salts is blended with atleast one excipient selected from fillers, disintegrants and binders;

• screening and sizing the prepared granules;

• treating the screened and sized granules with lubricants; and

• compressing the type I granules and type II granules to obtain layered tablets.

2. A process for the manufacture of composition as claimed in claim 1 wherein, layer-selective immediate release granules comprises of thiazolidinediones selected from Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts preferably Pioglitazone HCl present in amount from 5% to 30% by weight of the corresponding layer.

3. A process as claimed in claim 1 wherein,

• atleast 48%w/w and preferably over 50%w/w of the prolonged release granules comprise of Metformin HCl of particle size less than 100 microns;

• Metformin HCl is blended with one or more polymers selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, blending carried out in suitable mixer;

• Metformin HCl - polymer blend is wet granulated using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent being water or hydroalcoholic solution;

• the granulated mass is dried followed by sizing using comminuting mill or any other equipment suitable for the purpose, with appropriate mesh preferably around 1-mm mesh;

• the granules thus produced are mixed with talc, magnesium stearate and colloidal silicon dioxide.

4. A process as claimed in claim 1 and 2 wherein:

• the particle size of Pioglitazone HCl used is less than 30 microns;

• the Pioglitazone HCl is blended with fillers, disintegrants, binders, lubricants and permitted colours carried out in suitable mixer.

5. A process as claimed in claim 1, wherein the polymers used are preferably the mixture of alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid co-polymer, alginates or their pharmaceutically acceptable salts, xanthan gum and guar gum, preferably the mixture of one or more said celluloses with (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts and (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with xanthan gum or the mixture of one or more said celluloses with guar gum.

6. A process as claimed in claim 5, wherein the alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose is selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose, the (meth)acrylic acid co-polymer is selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt.

7. A process for the manufacture of the compositions as claimed in claim 6, wherein alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose are selected from methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose,

carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose present in an amount of atleast 35% by weight of the biguanide, more preferably 40-65 % by weight of the biguanide.

8. A process as claimed in claim 5 wherein the binary mixture of the polymers are selected from the mixture of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and Xanthan gum ; hydroxypropylmethylcellulose and guar gum; in the ratios ranging from 1 : 0.01 to 1 : 3.5.

9. A process as claimed in claim 5, wherein the mixture of three polymers is selected from hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer and hydroxypropylmethylcellulose, sodium alginate and methacrylic acid copolymer used in ratios of 1 : 0.01: 0.1 to 1 : 3.5 : 0.5 respectively.

10. A process as claimed in claims 1, 3, 5 – 6, 8 – 9, wherein the one or more polymers used is atleast 35% by weight of the biguanide, most preferably 40 – 65 % by weight of the biguanide.

11. A process as claimed in claims 1, 3, 5 – 9 for the preparation of the pharmaceutical compositions in multi-layered / bi-layered tablet wherein the nominal viscosity at 20°C of a 2% w/w aqueous solution of hydroxypropylmethylcellulose used is not less than 3000cP, the nominal viscosity of a 1%w/w aqueous solution of sodium alginate at 20°C is not less than 50cP and the nominal viscosity of a 1%w/w aqueous dispersion of guar gum is not less than 2000 cP.

12. A process as claimed in claims 1, 3, 5 – 9 for the preparation of the pharmaceutical compositions in multi-layered / bi-layered tablet wherein, the nominal viscosity at 25°C of a 1% w/w aqueous solution of hydroxypropylcellulose is not less than 1500cP; hydroxyethylcellulose is not less than 1500cP; sodium carboxymethylcellulose is not less than 1500 cP and xanthan gum is not less than 1200 cP.

13. A process as claimed in claims 1 and 4 wherein the disintegrating agents are selected from the group comprising starch, sodium starch glycollate, crosscarmellose sodium, crosspovidone, pregelatinized starch, microcrystalline cellulose, hydroxypropylcellulose.

14. A process for the composition as claimed in claim 1, wherein the immediate release layer is a mixture of from 5% to 30% by weight of the thiazolidinediones and from 1 to 10% by weight of biguanides with excipients and other formulation ingredients.

15. A process according to claims 2 – 4, wherein Metformin HCl is in the range of 500mg -2000mg and Pioglitazone HCl equivalent to Pioglitazone is in the range of 15 - 60 mg.

16. A process for the manufacture of composition as claimed in claim 1, wherein the layers of the tablet are parallel to each other.

17. A process according to claim 1, wherein, the multilayer tablet is enrobed by soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile.

18. An antihyperglycemic pharmaceutical composition as multi-layered tablet dosage form comprising atleast two layers wherein,
a) type I layer for pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts comprises atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide or its pharmaceutically acceptable salts; and
b) another layer for immediate release of active pharmaceutical ingredients (API) or APIs or their pharmaceutically acceptable salts selected from thiazolidinediones and sulfonyl ureas and atleast one excipient selected from fillers, disintegrants, binders and lubricants.

19. A pharmaceutical composition as claimed in claim 18, wherein the compressed layer containing biguanide and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts releases biguanide in the range of 25% – 45%, 50% – 80% and not less than 75% at the end of 1, 4, and 8 hours respectively.

20. A pharmaceutical composition as claimed in claim 18, wherein the compressed layer comprising API or APIs or their pharmaceutically acceptable salts releases not less than 80% of the said API or APIs or their pharmaceutically acceptable salts at the end of 30 minutes.

21. A pharmaceutical composition claimed in claims 18 – 20 wherein the prolonged release layer comprises of biguanide preferably Metformin HCl and the immediate release layer comprises of thiazolidinediones preferably Pioglitazone HCl with or without Metformin HCl.

22. A pharmaceutical composition as claimed in claim 21 wherein the immediate release layer comprises 5% to 30% by weight of thiazolidinediones and 1 to 10% by weight of Metformin HCl.

23. A pharmaceutical composition as claimed in claims 18 and 21 wherein, thiazolidinediones is selected from Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts preferably Pioglitazone HCl and biguanides are selected from Metformin, Buformin and Phenformin and their pharmaceutically acceptable salts preferably Metformin HCl.

24. A pharmaceutical composition as claimed in claim 18, wherein the immediate release API or APIs or their pharmaceutically acceptable salts are present in an amount of from 5% - 30% by weight of the immediate release layer.

25. A pharmaceutical composition as claimed in claims 18 and 19, wherein the polymers used are preferably the mixture of alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid co-polymer, xanthan gum, alginates or their pharmaceutically acceptable salts and guar gum, preferably the mixture of one or more said celluloses with (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts and (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with xanthan gum or the mixture of one or more said celluloses with guar gum.

26. A pharmaceutical composition as claimed in claim 25, wherein the alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose is selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose, the (meth)acrylic acid co-polymer is selected from esters of ethyl acrylate and methyl methacrylate, ethyl

ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt.

27. A pharmaceutical composition as claimed in claim 26, wherein alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose are selected from methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose present in an amount of atleast 35% by weight of the biguanide, more preferably 40-65 % by weight of the biguanide.

28. A pharmaceutical composition as claimed in claims 25 – 27 wherein, the binary mixture of the polymers are selected from the mixture of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and Xanthan gum; hydroxypropylmethylcellulose and guar gum; in the ratios ranging from 1: 0.01 to 1: 3.5.

29. A pharmaceutical composition as claimed in claims 25 – 27 wherein, the mixture of three polymers is selected from hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer and hydroxypropylmethylcellulose, sodium alginate and methacrylic acid copolymer used in ratios of 1 : 0.01: 0.1 to 1 : 3.5 : 0.5 respectively.

30. A pharmaceutical composition as claimed in claims 18 – 19, 25 – 29 wherein, the one or more polymers used is atleast 35% by weight of the biguanide, most preferably 40 – 65 % by weight of the biguanide.

31. A pharmaceutical dosage form comprising of type I granules as claimed in claims 1 and 18 wherein, the dosage form exhibits pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts comprising atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide preferably Metformin HCl.

Abstract:

A novel patient-convenient, cost effective pharmaceutical composition, comprising of thiazolidinediones and biguanide for controlling hyperglycemia manufactured as multilayer tablet and its process of manufacturing, for immediate release of thiazolidinediones or thiazolidinediones and biguanide and prolonged release of the biguanide only, the tablet comprising of minimum two layers wherein one outer layer comprises of a mixture of excipients and thiazolidinediones or thiazolidinediones and biguanide allowing immediate release of thiazolidinediones or thiazolidinediones and biguanide respectively and the other layer arranged in contact with the immediate release layer which comprises of a novel composition of excipients and a minimum one or more non-biodegradable, inert polymer(s) and the biguanide allowing pH independent prolonged release of the biguanide up to a period of 8-12 hours. The tablets are for once a day dosing. The tablets may optionally be film coated or enrobed by soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile.

Annex 2

PCT APPLICATION: PCT / IN02 / 00207

Applicant: Themis Laboratories Private Limited et. al.,

Applicants or Agents File Reference No. TLP / 533 / PCT1

Response To Second Opinion

With reference to paragraph 2.1 of the 2nd written opinion, we have rectified our errors in numbering the claims and claim dependencies. The claim numbers mentioned in this communication have been renumbered.

With reference to paragraph 2.2 of the 2nd written opinion, we have deleted claims 17, 18 and 20 and have amended claims 1, 22 – 25 and 30 to define the invention in terms of technical feature that contributes to the solving the problems faced.

With reference to paragraph 2.3 – 2.6 of the 2nd written opinion, we have deleted the terms **"inhibitors"** and **"enhancers".**

Term **"non-biodegradable inert polymers"** and **"cellulose derivatives"** have been replaced by specific class of cellulose derivatives that is **"alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose".**

With reference to paragraph 2.7 of the 2nd written opinion, the use of terms **"and / or", "but not limited to"** and **"such as"** have been deleted as advised in claims 1-3, 6, 25 and 28.

With reference to paragraph 2.7 of the 2nd written opinion, the use of word **"about"** has been deleted as advised in claims 2,9, 10, 15, 18 and 27.

With reference to paragraph 2.9 of the 2nd written opinion, the deficiencies in claims 1 and 3 have been rectified. It refers to '**type I granules comprises atleast 48% w/w of biguanide"**

With reference to paragraph 3.3 of the 2nd written opinion, we would like to inform you that in **Document D1,** the granules of Metformin HCl are not in a prolonged release form. This is further clear from the examples 1 – 3 on page 9 of D1, wherein the HPMC used is **maximum 6%w/w of Metformin HCl,** which is not sufficient to prolong the release of Metformin HCl, which is a highly water soluble drug.

It may be appreciated that in the present invention, the prolonged release of biguanide preferably Metformin HCl is achieved by utilizing one or more polymers selected from alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in the level of **atleast 35%** by weight of biguanide preferably Metformin HCl.

Written Explanation as Per Rule 66.8

The following pages have been incorporated as replacement sheets (Sheets, 18, 19, 21, 22, 23 and 24) on account of an amendment. The differences between the replaced sheets and the replacement sheets and the reasoned statements following the amendments are as follows.

Table indicating the page number on which amendments are done and replaced by replacement sheet

Original application	**First Amendment**	**Second Amended Specification**
Page No. 1– 3	-	AS ORIGINALLY FILED (Sheet not enclosed)
	Page No. 4	As 1st Amended Specification (sheet not enclosed)
Page No. 5–17	-	AS ORIGINALLY FILED (Sheet not enclosed)
-	**Page No. 18**	**Replaced by replacement sheet of page no. 18 as enclosed**
-	**Page No 19**	**Replaced by replacement sheet of page no. 19 as enclosed**
Page No. 20	-	**Replaced by replacement sheet of page no. 20 as enclosed**
-	**Page No 21**	**Replaced by replacement sheet of page no. 21 as enclosed**
-	**Page No 22**	**Replaced by replacement sheet of page no. 22 as enclosed**
New Sheet	-	**Page no. 23 as enclosed.**
Abstract on Page No. 23	-	**Replaced by replacement sheet of page no. 24 as enclosed**

A) The following amendments have been made in the claims of the **application as originally filed** and the claims of 1st **(first) amended specification** on 12th March 2004. The amended specification filed herewith along with this response will be referred hereafter as 2nd (second) **amended specification.**

1) **Claim 1** of the **first amended specification** on **page no. 18** has been replaced by

We Claim:

"A process for manufacture of antihyperglycemic pharmaceutical composition as multi-layered tablet dosage form for once a day administration comprising:

- preparation of type I granules for pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts wherein, the type I granules comprise atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns, blended with one or more polymers selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide or its pharmaceutically acceptable salts;
- preparation of type II granules for immediate release of active pharmaceutical ingredient (API) or APIs or their pharmaceutical acceptable salts selected from thiazolidinediones and sulfonyl ureas wherein, the said API or APIs or their pharmaceutical acceptable salts is blended with atleast one excipient selected from fillers, disintegrants and binders;
- screening and sizing the prepared granules;
- treating the screened and sized granules with lubricants; and
- compressing the type I granules and type II granules to obtain layered tablets."

This appears on **page no. 18 of the second amended specification as Claim 1** by way of correction, clarification and explanation. The present construction clearly brings out the novelty and inventive step.

(**Reference**: Lines 2 – 3 of claim 5 on page no. 18, Lines 1 – 2 of claim 9 on page no. 19, lines 7 – 8 of claim 10 on page no. 20 of the application as originally filed).

It may be noted that all the molecules falling under the class of Biguanides, Thiazolidinediones and Sulfonyl ureas including their pharmaceutically acceptable salts would result in successful reproduction of the invention disclosed in the application.

2) **Claim 2** of the **first amended specification** on **page no. 18** has been replaced by

"A process for the manufacture of composition as claimed in claim 1 wherein, layer-selective immediate release granules comprises of thiazolidinediones selected from

Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts preferably Pioglitazone HCl present in amount from 5% to 30% by weight of the corresponding layer."

This appears on **page no. 18 of the second amended specification as Claim 2** by way of correction, clarification and explanation.

3) **Claim 3** of the **first amended specification** on **page no. 18 – 19** has been replaced by

" A process as claimed in claim 1 wherein,

- atleast 48%w/w and preferably over 50%w/w of the prolonged release granules comprise of Metformin HCl of particle size less than 100 microns;
- Metformin HCl is blended with one or more polymers selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, blending carried out in suitable mixer;
- Metformin HCl - polymer blend is wet granulated using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent being water or hydroalcoholic solution;
- the granulated mass is dried followed by sizing using comminuting mill or any other equipment suitable for the purpose, with appropriate mesh preferably around 1-mm mesh;
- the granules thus produced are mixed with talc, magnesium stearate and colloidal silicon dioxide."

This appears on **page no. 18 – 19 of the second amended specification as Claim 3** by way of correction, clarification and explanation.

4) **Claim 4** of the **first amended specification on Page no. 19,** has been replaced by

"A process as claimed in claim 1 and 2 wherein:

- the particle size of Pioglitazone HCl used is less than 30 microns;
- the Pioglitazone HCl is blended with fillers, disintegrants, binders, lubricants and permitted colours carried out in suitable mixer."

This appears **on page no. 19 of the second amended specification as claim 4** by way of correction, clarification and explanation.

5) **Claim 5** of the **first amended specification on Page no. 19,** has been deleted, as the irrelevant claim in the **second amended specification** is superfluous.

6) **Claim 6** of the **first amended specification on Page no. 19,** has been replaced by

"A process as claimed in claim 1, wherein the polymers used are preferably the mixture of alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid co-polymer, alginates or their pharmaceutically acceptable salts, xanthan gum and guar gum, preferably the mixture of one or more said celluloses with (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts and (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with xanthan gum or the mixture of one or more said celluloses with guar gum."

This appears **on page no. 19 of the second amended specification** as **claim 5** by way of correction, clarification and explanation.

7) **Claim 7** of the **first amended specification on Page no. 19,** has been replaced by

"A process as claimed in claim 5, wherein the alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose is selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose, the (meth)acrylic acid co-polymer is selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt"

This appears **on page no. 19 of the second amended specification** as **claim 6** by way of correction, clarification and explanation.

8) **Claim 10** of the <u>application as originally filed on Page no. 20,</u>

"A process for the manufacture of compositions as claimed in claims 1,5, 7 – 9 wherein the cellulose derivatives are" and

" are incorporated in amount" is replaced by

"A process for the manufacture of the compositions as claimed in claim 6, wherein alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose are" and

"present in an amount" respectively by way of correction, explanation and clarification.

This appears in **claim 7 on page no. 19 and 20 of the second amended specification.**

9) **Claim 11** of the **application as originally filed on page no. 20**, "A process as claimed in claims 1, 5, 7 - 10 wherein the binary combinations of the polymers are selected from combinations of" **and** "ratios ranging from about 1 : 0.01 to about 1 : 3.5" is replaced by **"A process as claimed in claim 5 wherein the binary mixture of the polymers are selected from the mixture of"** and **"in the ratios ranging from 1 : 0.01 to 1 : 3.5"** respectively by way of correction, clarification and explanation.
This appears in **claim 8 on page no. 20 of the second amended specification.**

10) **Claim 12** of the **application as originally filed on page no. 20**, has been replaced by "A process as claimed in claim 5, wherein the mixture of three polymers is selected from hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer and hydroxypropylmethylcellulose, sodium alginate and methacrylic acid copolymer used in ratios of 1 : 0.01: 0.1 to 1 : 3.5 : 0.5 respectively".
This appears **on page no. 20 of the second amended specification** as **claim 9** by way of correction, clarification and explanation.
Reference: Lines 3 – 4 of claim 8 on page no. 19 of the application as originally filed.

11) **Claim 13** of the **application as originally filed on page no. 20**, "A process as claimed in claims 1, 5, 7 - 12 wherein the polymers used is" is replaced by "**A process as claimed in claims 1, 3, 5 – 6, 8 – 9, wherein the one or more polymers used is"** by way of clarification, explanation and correction.
This appears in **claim 10 on page no. 20 of the second amended specification.**

12) **Claim 14** of the **application as originally filed on page no. 22**, **"**A process as claimed in claims 1, 5, 7 – 13 for the preparation of the antihyperglycemic pharmaceutical compositions in" is replaced by "**A process as claimed in claims 1, 3, 5 – 9 for the preparation of the pharmaceutical compositions in"** by way of clarification, explanation and correction.
This appears in **claim 11 on page no. 20 of the second amended specification.**

13) **Claim 15** of the **application as originally filed on page no. 22 – 23**, "A process as claimed in claims 1, 5, 7 - 13, wherein for the preparation of the antihyperglycemic pharmaceutical compositions in" is replaced by **"A process as claimed in claims 1, 3, 5 – 9 for the preparation of the pharmaceutical compositions in"** by way of clarification, explanation and correction.
This appears in **claim 12 on page no. 20 of the second amended specification.**

14) **Claim 14** of the **first amended specification on page no. 21,** "A process as claimed in claims 1, 4, 6 wherein" is replaced by **"A process as claimed in claims 1 and 4 wherein"** by way of clarification and correction.
This appears in **claim 13 on page no. 20 of the second amended specification.**

15) **Claim 15** of the **first amended specification on page no. 21** has been replaced by "A process for the composition as claimed in claim 1, wherein the immediate release layer is a mixture of from 5% to 30% by weight of the thiazolidinediones and from 1 to 10% by weight of biguanides with excipients and other formulation ingredients."
This appears on **page no. 21 of the second amended specification as Claim 14** by way of correction, clarification and explanation.

16) **Claim 16** of the **first amended specification on page no. 21, "**A process according to claims 1, 4 - 6 where" is replaced by **"A process according to claims 2 – 4, wherein"** by way of clarification and correction.
This appears in **claim 15 on page no. 21 of the second amended specification.**

17) **Claims 17, 18 and 20** of the **first amended specification on page no. 21 have been deleted**.

18) **Claim 19** of the **first amended specification on page no. 21,** "claims 1, 4 – 20 wherein" is replaced by **"claim 1, wherein"** by way of clarification and correction.
This appears in **claim 16 on page no. 21 of the second amended specification.**

19) **Claim 21** of the **first amended specification on page no. 21,** "claims 1, 4 – 22 wherein" is replaced by "**claim 1, wherein**" by way of clarification and correction.
This appears in **claim 17 on page no. 21 of the amended specification.**

20) **Claim 22** of the **first amended specification on page no. 21** has been replaced by "A pharmaceutical composition as claimed in claim 18, wherein the compressed layer containing biguanide and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts releases biguanide in the range of 25% – 45%, 50% – 80% and not less than 75% at the end of 1, 4, and 8 hours respectively."
This appears on **page no. 21 of the second amended specification as Claim 19** by way of correction, clarification and explanation.

21) **Claim 23** of the **first amended specification on page no. 22** has been replaced by "A pharmaceutical composition as claimed in claim 18, wherein the compressed layer comprising API or APIs or their pharmaceutically acceptable salts releases not less than 80% of the said API or APIs or their pharmaceutically acceptable salts at the end of 30 minutes."
This appears on **page no. 22 of the seond amended specification as Claim 20** by way of correction, clarification and explanation.

22) **Claim 24** of the **first amended specification** on **page no. 22** has been replaced by "An antihyperglycemic pharmaceutical composition as multi-layered tablet dosage form comprising atleast two layers wherein,
a) type I layer for pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts comprises atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide or its pharmaceutically acceptable salts; and
b) another layer for immediate release of active pharmaceutical ingredients (API) or APIs or their pharmaceutically acceptable salts selected from thiazolidinediones and sulfonyl ureas and atleast one excipient selected from fillers, disintegrants, binders and lubricants."

This appears on **page no. 21 of the second amended specification as Claim 18** by way of correction, clarification and explanation. The present construction clearly brings out the novelty and inventive step.

23) **Claim 25** of the **first amended specification** on **page no. 22** has been replaced by "A pharmaceutical composition claimed in claims 18 – 20 wherein the prolonged release layer comprises of biguanide preferably Metformin HCl and the immediate release layer comprises of thiazolidinediones preferably Pioglitazone HCl with or without Metformin HCl."
This appears on **page no. 22 of the second amended specification as Claim 21** by way of correction, clarification and explanation.

24) **Claim 26** of the **first amended specification** on **page no. 22** has been replaced by

"A pharmaceutical composition as claimed in claim 18, wherein the immediate release API or APIs or their pharmaceutically acceptable salts are present in an amount of from 5% - 30% by weight of the immediate release layer."
This appears on **page no. 22 of the second amended specification as Claim 24** by way of correction, clarification and explanation.

25) **Claim 27** of the **first amended specification** on **page no. 22** has been replaced by "A pharmaceutical composition as claimed in claim 21 wherein the immediate release layer comprises 5% to 30% by weight of thiazolidinediones and 1 to 10% by weight of Metformin HCl."
This appears on **page no. 22 of the second amended specification as Claim 22** by way of correction, clarification and explanation.

26) **Claim 28** of the **first amended specification** on **page no. 22** has been replaced by "A pharmaceutical composition as claimed in claims 18 and 21 wherein, thiazolidinediones is selected from Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts preferably Pioglitazone HCl and biguanides are selected from Metformin, Buformin and Phenformin and their pharmaceutically acceptable salts preferably Metformin HCl. "
This appears on **page no. 22 of the second amended specification as Claim 23** by way of correction, clarification and explanation.
References: Claim 2 on page no. 18 and Lines 18 –2 1 on page no. 8 of the application as originally filed.

27) **Claim 29** of the **first amended specification** on **page no. 22** has been deleted, as the irrelevant claim in the **second amended specification** is superfluous.

28) **Claim 30** of the **first amended specification** on **page no. 22** has been replaced by "A pharmaceutical dosage form comprising of type I granules as claimed in claims 1 and 18 wherein, the dosage form exhibits pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts comprising atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide preferably Metformin HCl".

This appears on **page no. 23 of the second amended specification as Claim 31** by way of correction, clarification and explanation.

29) **New claim - Claim 25** on **page no. 22** has been added to read as:

"A pharmaceutical composition as claimed in claims 18 and 19, wherein the polymers used are preferably the mixture of alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid co-polymer, xanthan gum, alginates or their pharmaceutically acceptable salts and guar gum, preferably the mixture of one or more said celluloses with (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts and (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with xanthan gum or the mixture of one or more said celluloses with guar gum."

30) **New claim - Claim 26** on **page no. 22 – 23** has been added to read as

"A pharmaceutical composition as claimed in claim 25, wherein the alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose is selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose, the (meth)acrylic acid co-polymer is selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt."

31) **New claim - Claim 27** on **page no. 23** has been added to read as

"A pharmaceutical composition as claimed in claim 26, wherein alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose are selected from methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose present in an amount of atleast 35% by weight of the biguanide, more preferably 40-65 % by weight of the biguanide."

32) **New claim - Claim 28** on **page no. 23** has been added to read as

"A pharmaceutical composition as claimed in claims 25 – 27 wherein, the binary mixture of the polymers are selected from the mixture of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and Xanthan gum; hydroxypropylmethylcellulose and guar gum; in the ratios ranging from 1: 0.01 to 1: 3.5."

33) **New claim** - Claim 29 on page no. 23 has been added to read as

" A pharmaceutical composition as claimed in claims 25 – 27 wherein, the mixture of three polymers is selected from hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer and hydroxypropylmethylcellulose, sodium alginate and methacrylic acid copolymer used in ratios of 1 : 0.01: 0.1 to 1 : 3.5 : 0.5 respectively."

34) **New claim - Claim 30** on **page no. 23** has been added to read as

"A pharmaceutical composition as claimed in claims 18 – 19, 25 – 29 wherein, the one or more polymers used is atleast 35% by weight of the biguanide, most preferably 40 – 65 % by weight of the biguanide."

Basis of addition of new claims:

The pharmaceutical composition of the present invention comprises of Type I layer for prolonged in-vitro release of biguanide preferably Metformin HCl. Type I layer further comprise of polymer(s) selected from alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts present in the amount and in the ratios as mentioned in the claims 25 - 30

References: Claims 7 – 9 on page no. 19 and claims 10 – 13 on page no. 20 of the application as originally filed

Lines 21 – 31 on page no. 11, lines 1 – 10, 22 – 27 on page no. 12 of the application as originally filed.

35) Abstract on page no. 23 of the application as originally filed replaced by Abstract on page no. 24 of **the second amended specification.**

No change in the text matter of the abstract